#22 PATENT 2-12-03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



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| In re Application of: ZHANG et al. | Examiner: R. Shukla |
| | Group Art Unit: 1632 |
| For: METHODS AND COMPOSITIONS FOR SCREENING FOR ANGIOGENESIS-MODULATING COMPOUNDS | Confirmation No. 9639 |
| Serial No.: 09/465,978 | **RESPONSE TO OFFICE COMMUNICATION** |
| Filed: December 16, 1999 | |
| Atty. Dkt.: PXE-012.US (9400-0003.20) | |

Commissioner for Patents
Washington, D.C. 20231

Sir:

This paper is filed in response to the Office Communication dated December 17, 2002, for which a one-month shortened statutory period for reply was set. Thus, this paper is timely filed and no fee is due.

The Communication indicates that Applicants' response, filed on September 10, 2002, was not fully responsive. In particular, it was alleged that Applicants were not fully responsive because the objection to the brief description of the drawings as stated on page 2 of the Office Action (mailed March 13, 2002) was not addressed.

Applicants would be happy to address any remaining issues. However, they have been unable to find any objections raised to the brief description of the drawings in the previous Office Action (copy attached hereto). Applicants left a telephone message on January 17, 2003 to Examiner Shukla in order to clarify the situation, but were unsuccessful in contacting him. Applicants invite the Examiner to contact their undersigned representative to discuss this issue further.

Respectfully submitted,

Date: 17 Jan 03

By: Dahna S. Pasternak

Dahna S. Pasternak
Registration No. 41,411

Cooley Godward LLP
Five Palo Alto Square
3000 El Camino Real
Palo Alto, CA 94306
Tel.: (650) 843-5608; Fax: (650) 857-0663

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/465,978 | 12/16/1999 | NING ZHANG | PXE-012.US | 9639 |

20855 7590 03/13/2002

ROBINS & PASTERNAK LLP
545 MIDDLEFIELD ROAD
SUITE 180
MENLO PARK, CA 94025

| EXAMINER |
|---|
| SHUKLA, RAM R |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | 18 |

DATE MAILED: 03/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.



DOCKETED GRF

9400-0003.20
RS 6/13/02
LD 9/13/02

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/465,978 | ZHANG ET AL. | |
| | Examiner | Art Unit | |
| | Ram Shukla | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *28 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.



**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

## DETAILED ACTION

1. Applicant's election of the invention of group I, claims 1-14 in Paper No. 17 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Keeping in view the compact prosecution and customer service, the amendment canceling claims 1-27 has been entered as requested by the applicant.

3. New claims 28 and 29 have been entered.

Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at www.uspto.gov).

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 28 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at www.uspto.gov).

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. Since it is not realistic to expect that the "complete structure" of any transgenic animal, or even a cell, could be described, this requirement is interpreted to be whether phenotypic consequences of altering the genotype have been described. In the instant case, the claimed invention

encompasses a transgenic mouse comprising a transcription regulator operably linked to a reporter sequence encoding a light-generating protein, wherein the transcription regulator consists of the sequence of SEQ ID NO: 32. In terms of describing the invention, the specification provides prophetic example of generating transgenic mice carrying vectors described in the specification, how to screen for ES cells that were positive for vector integration by homologous recombination, and how to screen for chimeric mice based on coat color and methodology to make transgenic animals (see pages 69-73). However, the specification does not describe the phenotype and characteristics of the transgenic mice that comprised the recited construct. The specification does not provide any description as to whether all the cells of the transgenic mice would express the reporter gene or whether a certain cell type would express the reporter gene and what would be the effect of expressing the transgene on the transgenic mice development. It is noted that the applicants have submitted 1.132 declaration by the inventor describing the making of a transgenic mice that represent the transgenic mice encompassed by the claimed invention, however the mice was made using a vector in which the expression of the reporter protein luciferase was under the control of SEQ ID NO 32 and a VEGFR-2 enhancer (see last paragraph on page 2). In the last paragraph on page 3 of the declaration, applicants have noted that the transgenic mice containing SEQ ID N32 expressed high level of luciferase activity in the entire body when 1 week old, and the activity declined rapidly (by up to 7000 fold) over time and by 6 week after birth, the luciferase activity dropped to a basal level and that VEGFR-2 expression can be monitored in transgenic mice. It is note clear whether the transgenic mice which was made using the transcription regulator of SEQ I DNO 32 alone (without the enhancer) would have had the same phenotype. The specification neither describes these characteristics nor it discloses as to what characteristics could be expected in the mouse and whether the characteristics observed in the transgenic mice of the declaration were to be expected. In other words, with the limited information disclosed in the specification, an artisan would have not been able to predict whether the phenotype of the recited transgenic mice.

Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the transgenic mouse recited in the claims at the time the application was filed.

6. Claims 28 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

In the instant case, the claimed invention encompasses a transgenic mouse comprising a transcription regulator operably linked to a reporter sequence encoding a light-generating protein, wherein the transcription regulator consists of the sequence of SEQ ID NO: 32. Claim 29 limits the reporter protein to luciferase. First the question is, with the disclosure provide at the time of filing, could an artisan of skill make the recited transgenic mouse? The specification teaches how to make a VEGFR-2 targeting vector for making the transgenic mice (see pages 67). The specification also discloses prophetic example of generating transgenic mice carrying vectors described in the specification, how to screen for ES cells that were positive for vector integration by homologous recombination, and how to screen for chimeric mice based on coat color and methodology to make transgenic animals (see pages 69-73). It is noted that the specification teaches to insert a VEGFR-2 enhancer sequence to the vector comprising the SEQ ID NO 32 and use the resultant vector in making a transgenic mouse. Therefore, it is not clear whether a transgenic mouse recited in claim 28 could have been made that expressed the reporter protein in the absence of the enhancer of the VEGFR-2. However, the specification does not describe the phenotype and characteristics of the transgenic mice that comprised the recited construct. The specification does not provide any description as to whether all the cells of the transgenic mice would express the reporter gene or whether a certain cell type would express the reporter gene and what would be the effect of expressing the transgene on the transgenic mice development. While the art of making a transgenic mouse has become routine and therefore, an artisan would have been able to make the transgenic mouse as claimed, the next question is, in the absence of any phenotype or characteristics, would an artisan of skill have been able to use the claimed transgenic mouse.

It is noted that the applicants have submitted 1.132 declaration by the inventor describing the making of a transgenic mice that represent the transgenic mice encompassed by the claimed invention, however the mice was made using a vector in which the expression of the reporter protein luciferase was under the control of SEQ ID NO 32 and a VEGFR-2 enhancer (see last paragraph on page 2). In the last paragraph on page 3 of the declaration, applicants have noted that the

transgenic mice containing SEQ ID N32 expressed high level of luciferase activity in the entire body when 1 week old, and the activity declined rapidly (by up to 7000 fold) over time and by 6 week after birth, the luciferase activity dropped to a basal level and that VEGFR-2 expression can be monitored in transgenic mice. It is note clear whether the transgenic mice which was made using the transcription regulator of SEQ I DNO 32 alone (without the enhancer) would have had the same phenotype. The specification neither describes these characteristics nor it discloses as to what characteristics could be expected in the mouse and whether the characteristics observed in the transgenic mice of the declaration were to be expected. It is noted that for an artisan would have required the characteristics of the transgenic mice for its intended use in identifying compounds that alter angiogenesis or that alter the expression of VEGFR-2 promoter, however, in the absence of any guidance regarding the phenotype of the mouse, an artisan would not have been able to use the mouse. Furthermore, since the targeting vector contains a reporter gene, its insertion in the genome of the mice would result in the disruption of the expression of the VEGFR-2 protein and it is not clear as to what would be the effect of the loss of VEGFR-2 protein on the transgenic mouse. Wood (Comparative Medicine 50 (1): 12-15, 2000) noted:

"The phenotype of an animal is determined by a complex interaction of genetics and environment. It is the evaluation of the phenotype that allows us to determine the usefulness of a mutant strain as a model for biomedical research.....A specific phenotype is usually expected from genetically altered mice whether they are transgenic over-expression models or gene knockout models where a particular gene function has been modified or ablated altogether. Thus for any given genetic alteration, we often try to predict what the phenotype will be. Many times we find the predicted phenotypes or more. It is, however, common to hear that surprisingly a given model has "no phenotype"."

This clearly indicates that the phenotype of the transgenic mice is unpredictable and the specification does not provide any guidance regarding the phenotype of the claimed transgenic mouse and therefore, an artisan of skill would have required extensive experimentation to determine the effects of expressing the

vector construct comprising SEQ ID NO 32 and to use them in screening for compounds that altered angiogenesis and such experiments would have been undue since the phenotype of transgenic mice unpredictable.

***Double Patenting***

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 28 and 29 are provisionally rejected under the judicially created doctrine of double patenting over claim 14 of co-pending Application No. 09/738,968. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced co-pending application and would be covered by any patent granted on that co-pending application since the referenced co-pending application and the instant application are claiming common subject matter, as follows: It is noted that the transgenic rodent of claim 14 of the co-pending application 09/738,968 would encompass the transgenic mouse of claim 29 of the instant application since the vector of claim 6 of the co-pending application would encompass the vector used for making the transgenic mouse of claim 29 of the instant application. It is noted that the polynucleotide of claim 3 (comprised in the vector of claim 6) of the co-pending application recites a polynucleotide that have greater than 80% sequence identity with the sequence of SEQ ID NO: 32.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other co-pending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

9. No claim is allowed.

Applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c) and a copy of all the pending/under consideration claims. For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (703) 305-3388.

RAM R. SHUKLA, PH.D
PATENT EXAMINER

Ram R. Shukla, Ph.D.

1632

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**Attorney Docket No. PXE-012.US (9400-0003.20)** **PATENT**

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Commissioner for Patents, Washington, D.C. 20231 on January 17, 2003.

By: Diane Kizer
Diane Kizer



# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of ZHANG et al.

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|---|---|---|---|
| Serial No.: | 09/465,978 | Examiner: | R. Shukla |
| Filed: | December 16, 1999 | Art Unit: | 1632 |

For: **METHODS AND COMPOSITIONS FOR SCREENING FOR ANGIOGENESIS-MODULATING COMPOUNDS**

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Commissioner for Patents
Washington, D.C. 20231

## TRANSMITTAL OF RESPONSE

Enclosed are the following documents in response to the Office Communication mailed December 17, 2002 for the above-identified application:

- [x] Amendment/Response
- [x] Copy of the previous Office Action dated March 13, 2002
- [x] Return receipt postcard
- [x] No fee required

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 03-3117.

Dated: 17 Jan 03

Respectfully submitted,
**COOLEY GODWARD LLP**

By: Dahna S. Pasternak
Dahna S. Pasternak
Reg. No. 41,411

Cooley Godward LLP
ATTN: Patent Group
Five Palo Alto Square
3000 El Camino Real
Palo Alto, CA 94306-2155
Tel: (650) 843-5000 Fax: (650) 857-0663

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